Food and Agriculture Organization of the United Nations

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FMD Technical Bulletin

Food and Agriculture Organisation of the United Nations Initiative: Assistance to Zimbabwe with development of an updated foot and mouth disease control strategy

(Part of a wider regional project aimed at development of non-geographic approaches to management of FMD trade-risk through application of commodity-based trade)

Prophylactic vaccination against SAT serotype foot and mouth disease in southern Africa

Background

Vaccination against FMD – especially the SAT serotypes – has a chequered history marked by outstanding successes, perhaps best exemplified by elimination of FMD from the European Union mainly through mass vaccination and accompanying zoo-sanitary measures up to 1991 (Leforban & Gerbier, 2002). There have also been failures illustrated by the situation in southern Africa where despite routine mass vaccination programmes conducted over more than 40 years, FMD outbreaks in cattle have not only escalated over the last decade-and-a-half but have also mostly occurred in routinely vaccinated populations (Thomson et al., 2013; OIE, 2016).

Clearly there are a number of possible explanations for the southern African experience, which is unlikely to be due to a single factor. Therefore, more careful evaluation of this problem is long overdue, not least in the case of Zimbabwe where over the last three years around $ 10 million has been spent on FMD vaccine and related purchases with little if any decline in outbreak incidence (E. Zanamwe -Sikala, personal communication, 2016).

Two aspects need to be considered where vaccination to reduce the occurrence of FMD in livestock in high-risk areas is applied, particularly in areas where naturally infected African buffalo constitute the major source of infection: (1) technical characteristics of currently available FMD vaccines and (2) logistical and financial considerations associated with vaccine administration.

Technical aspects

All vaccines used against FMD are currently inactivated, i.e. so-called 'killed' vaccines. Inactivated vaccines generally have a major positive attribute in that as long as their manufacture is adequately controlled and audited they are 'safe', i.e. have negligible potential for causing the disease against which they are directed. Attenuated or 'live' vaccines, on the other hand, are potentially more risky because viruses in vaccine can sometimes 'revert to virulence' or recombine with other viruses as they are capable of replication and therefore mutation and/or genetic recombination. Moreover, early experience with attenuated FMD vaccines was that it is difficult to determine the potential pathogenicity (i.e. possible disease-causing effects) of such vaccines in all species and classes of animals in which they may be used. Nevertheless, there is renewed interest in, and research into, attenuated FMD vaccines (GFRA Newsletter, 2016). New-generation vaccines based on recombinants or chemical synthesis of antigens (i.e. antigenic sites on the surface of the virus particle) have been extensively researched but initially promising results could not be effectively exploited on a commercial scale. A possible exception is a human adenovirus into which genetic material coding for FMD virus surface proteins has been cloned; this vaccine is undergoing field trials at present, including in Africa (www.reeis.usda.gov/web/crisprojectpages/0408929-novel-recombinant-adenovirus-vaccine-and-antiviral-vectors-to-control-fmdv.html).

A disadvantage of inactivated vaccines is that they require high doses of antigenic material to induce an effective immune response and the immune response following a single inoculation is often of limited duration (this has been found by some researchers to be a particular problem with SAT serotype vaccines). Therefore, each animal needs to be vaccinated repeatedly to achieve and maintain an adequate level of immunity (Knight-Jones et al., 2016). The net result is that prophylactic vaccination against FMD generally, particularly in the case of SAT viruses, is a logistically complicated and expensive undertaking (see below).

Functionality of FMD vaccines

Fundamental to understanding vaccination against FMD is that currently available vaccines do not protect effectively against infection (which usually occurs via inspiration of infected aerosols into the upper respiratory tract of cattle) or persistence of infection in the oro-pharyngeal (throat)

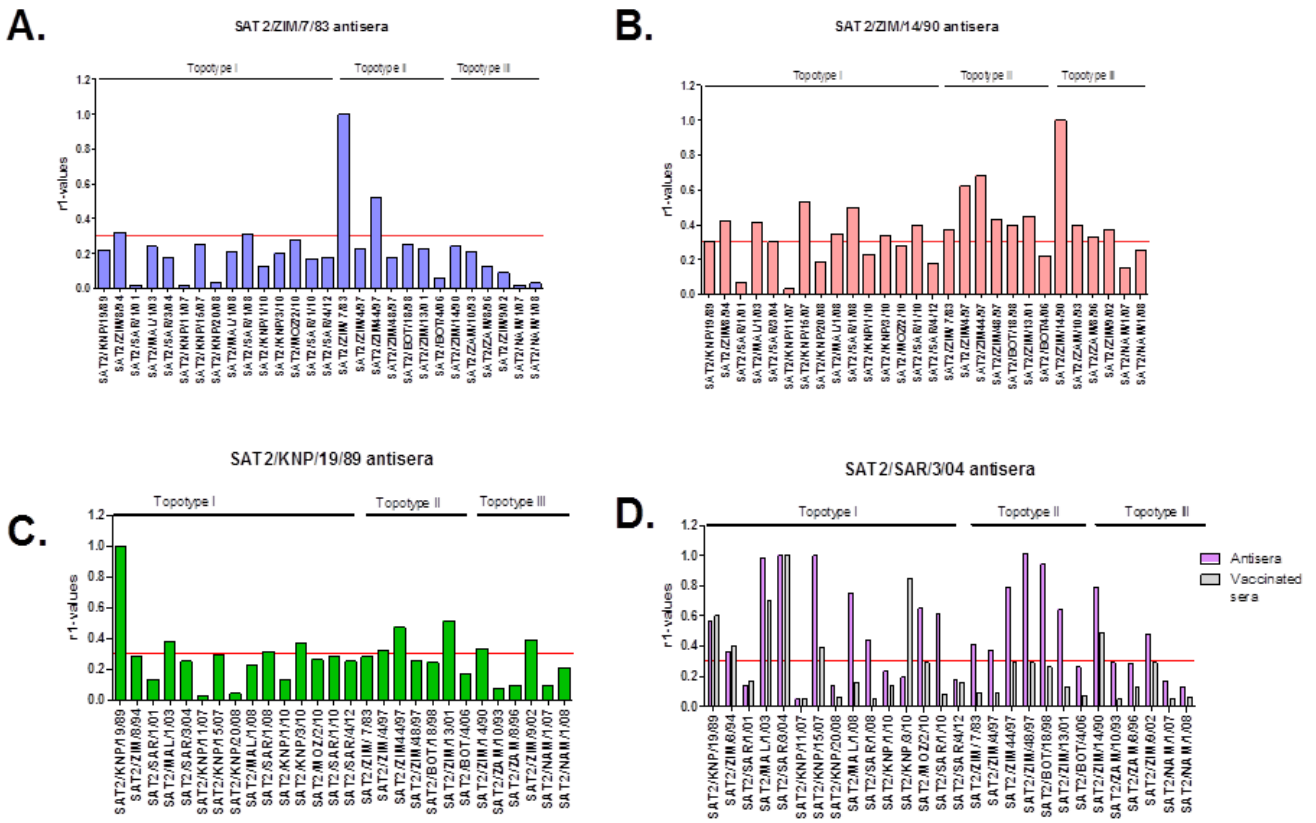

Figure 1: Reactions between SAT 2 viruses belonging to only 3/14 topotypes and antisera to four potential SAT 2 vaccine strains (one from Zimbabwe)

Note: The horizontal red line denotes a r-value of 0.3. Many of the bars do not reach 0.3, showing that the protection likely to be afforded by vaccines containing these vaccine strains is variable, even within topotypes.

Acknowledgement: Dr F Maree – ARC Onderstepoort Veterinary Institute, South Africa

mucosa (lining) and associated lymphatic tissue. Instead, they prevent the development of disease in animals that have been infected by preventing spread of the virus from the primary site of infection in the respiratory tract to secondary sites such as the mouth, feet and udder. Circulating antibody alone is capable of preventing secondary spread of infection, i.e. other immune mechanisms such as cellular- and cell-mediated immunity are apparently unimportant in the prevention of secondary spread. Therefore it is relatively easy to establish whether an animal will be resistant to disease development or not by measuring the level of circulating antibody induced by vaccination. This enables the performance of vaccines to be measured (see below).

A second important point is that effective vaccination reduces viral shedding by animals that have been well vaccinated but nevertheless become infected and thereby reduces the spread of infection between cattle in a herd exposed to infection (Parthiban et al., 2015). For that reason, if herd immunity levels >70% are achieved, outbreaks of FMD are prevented and the infection in that population will quickly die out. This is unlike the immunity generated by some other vaccines, rinderpest vaccine for example, where vaccinated animals are refractory to infection.

It should be remembered that in the grand scheme of vaccinology, FMD vaccines in general, and SATs particularly, are far from ideal vaccines and allowances need to be made for their imperfections.

The effect of antigenic diversity within SAT serotypes

SAT viruses – as already explained in FMD Bulletin # 1 – are more genetically and antigenically diverse than Eurasian serotypes with the possible exception of serotype A viruses (Thomson & Bastos, 2004; Maree et al., 2016). Therefore ensuring a satisfactory 'match' between SAT viruses circulating in the field and vaccine strains incorporated into commercially available vaccines is difficult with current technology. Antigenic diversity between SAT2 virus topotypes is illustrated in Figure 1 (see above).

For each of the three SAT serotypes, three or four topotypes occur in the southern African region and these are all probably present in Zimbabwe. Moreover, not all variants within a topotype cross protect effectively against each other (Figure 1). This means that there is no assurance that currently available vaccines will be effective against all SAT variants circulating in the field in Zimbabwe.

To get over this problem it has long been the desire to manufacture vaccines against specific isolates recovered from the field, i.e. to produce vaccines that are 'tailor-made' for specific locations. That well-intentioned desire is, unfortunately, still far from reality because the adaption of SAT field isolates as vaccine strains is only successful in a small minority of cases and is also time-consuming. Therefore, purchase of tailor-made SAT vaccines is currently no more than a long-term possibility.

For Eurasian serotypes antigenic variation is less problematic than for the SATs because of the existence of well characterised subtypes. Subtypes are groups of immunologically related viruses within a serotype that induce production of antibodies that have been shown to be effective against lineages of Eurasian FMD viruses; this aids rapid and effective deployment of appropriate vaccine in many situations. For SAT viruses no subtypes have yet been defined.

This means that the degree of protection afforded by currently available vaccine against the 4 SAT serotype lineages that were shown to be circulating in cattle in Zimbabwe in 2015 is uncertain (see FMD Bulletin # 1). On the other hand, the recent experience of Zimbabwe's DVS has been that vaccines used in the field have generally performed satisfactorily, although this has not been validated by field data.

Theoretically the problem of antigenic variation can be ameliorated by the use of more 'potent' vaccines, i.e. vaccine that contains a higher payload of antigens because such vaccines ($PD_{50} \geq 6$) tend to generate a broader immune response than conventional ($PD_{50} \geq 3$) vaccines. However, high potency vaccines, which were originally developed for use in outbreak situations where a fast-developing immune response is paramount, are expensive and potentially difficult to procure (see below).

The level of the 'match' between field viruses and vaccine strains included in FMD vaccines is generally measured by what is known as the 'r-value', which lies between 0-1; a value of 1 indicates immunological identity while 0 denotes zero identity. It is generally accepted that for a vaccine to be effective in a particular locality the r-value needs to be ≥0.3 against each of the field viruses present in that locality.

Objectives of vaccination against FMD

The ultimate objective of prophylactic vaccination is to generate herd immunity levels greater than 70% because in such circumstances, although individual animals may become infected, outbreaks of disease do not occur (as long as the 'match' between the vaccine strains and field viruses to which cattle in the field are exposed is satisfactory).

As usually applied in southern Africa, SAT vaccines are mostly used for prevention of FMD outbreaks in cattle in high-risk areas, the risk being defined by proximity to and interaction with African buffalo infected with SAT viruses. This is complicated by the fact that buffalo populations in different localities are generally associated with different topotypes of all three SAT serotypes (Thomson & Bastos, 2004).

Vaccines are also commonly used in southern Africa to hasten the resolution of outbreaks in cattle. However, the principles according to which this is done seem to vary between countries and there is little apparent consensus on the fundamentals of the approach. That issue is being addressed by recommendations for improved FMD outbreak management in Zimbabwe proposed by this FAO supported initiative.

Administration, cost and logistics of vaccination against SAT serotype FMD

Only cattle are vaccinated in most locations because experience has shown that cattle are more susceptible to infection and subsequent disease development than other cloven-hoofed domestic livestock. Species of livestock other than cattle have only rarely been implicated in FMD outbreaks in southern Africa although in recent years suspicion has been cast on goats but so far without credible scientific evidence available in the public domain.

Traditionally, routine mass prophylactic vaccination against FMD in southern African countries has been conducted biannually, i.e. every six months. The problem with this approach is that to establish a satisfactory 'primary immune response', 6 month-old cattle (younger animals are usually not vaccinated in endemic areas because they may have maternally-derived antibodies that interfere with the immune response to vaccination) need initially to receive two vaccinations about a month apart (range 2-8 weeks) and thereafter be re-vaccinated at 4-monthy intervals until they are at least two years of age. Cattle older than two years, if they have been vaccinated according to this schedule, need to be revaccinated at 6-monthly intervals while cattle above 4-5 years generally require only annual revaccination. This implies that cattle between 6-24 months of age need to be vaccinated 5-6 times, which is not only prohibitively expensive but also logistically complicated when it comes to large cattle populations raised in extensive rangeland systems.

Typical antibody responses of cattle vaccinated with inactivated FMD vaccines is illustrated in Figure 2a. However, if the relationship between strains of FMD virus incorporated into the vaccine and field viruses in circulation – essentially viruses maintained by buffalo in the locality – is not adequate (r-value <0.3) the likelihood of generating an effective immune response to the vaccine is low as illustrated in Figure 2b.

What often occurs in the field is that large numbers of animals in high risk areas are vaccinated irregularly (generally only

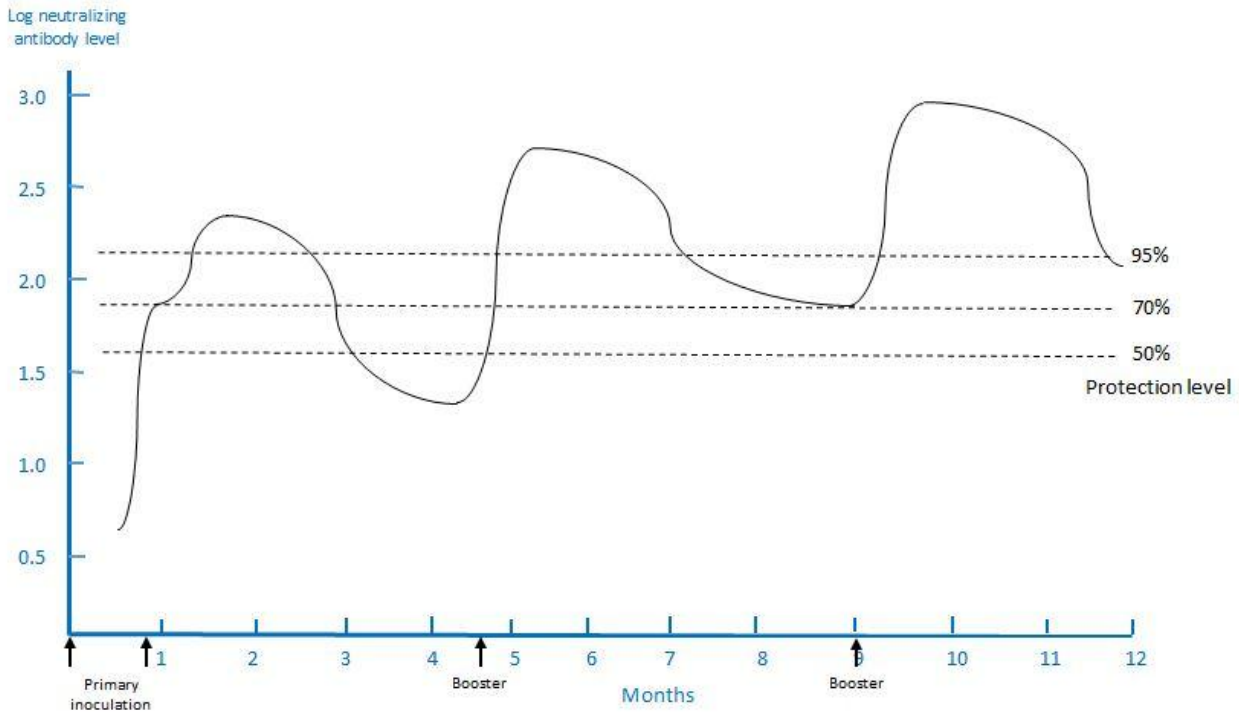

Figure 2a: Graphic representation of approximate antibody responses to FMD vaccination of naïve cattle (i.e. those without maternal immunity or previous infection), assuming an r-value of 1 **After: Pay, 1984**

when money is available to buy vaccine). As a rule of thumb it is far more effective to vaccinate fewer animals at the prescribed frequency than larger numbers of animals irregularly. The latter practise is essentially a waste of time and money and may even contribute to creating a competitive advantage for field viruses that are not 'matched' by vaccine strains included in the vaccine (see below).

The current purchase price of conventional SAT-type vaccines in use in Southern Africa is around US$ 2 per dose, i.e. much higher than is the case for Eurasian serotype vaccines applied in other regions of the world. This is not to infer that SAT vaccines are unjustifiably expensive; there are reasons for the disparity. Firstly, the SAT vaccine market is much smaller than for O, A and Asia 1 serotypes, rendering the unit cost of production high. Secondly, a number of technical aspects present a greater challenge to the manufacture of SAT vaccines than is the case for other serotypes. These include difficulty in developing vaccine strains that are structurally stable during vaccine manufacture as well as producing vaccines that are effective against the wide antigenic diversity that exists for SAT serotypes, especially SAT2.

Vaccine formulation and handling

Currently available vaccines against FMD viruses contain concentrated suspensions of vaccine strains that have been inactivated with an aziridine compound, associated with an adjuvant. The latter commonly comprises saponin (a tree-bark extract with surface-active properties) and alhydrogel (essentially aluminium hydroxide). Alternatively, various oil adjuvants are used instead of saponin/alhydrogel.

The relative efficacy of FMD vaccine formulations with the above-mentioned types of adjuvant has been a matter of debate for some decades now; it is claimed that oil-based adjuvants induce longer-lasting antibody responses than those formulated with alhydrogel-saponin adjuvants and therefore need to be applied less frequently. However, hard data on this issue are strangely hard to come by.

Whatever the case, it needs to be borne in mind that FMD vaccines need to be stored and handled in ways that maintain the vaccine in a cold environment (ideally 4° C +/- 2° C), i.e. the cold-chain needs to be maintained. It is also important that FMD vaccines are never frozen because that will destroy the inactivated virus/adjuvant complex that is important to the functionality of both saponin/alhydrogel- and oil-adjuvanted vaccines.

The advisability of using automatic syringes is a point of contention because they can lead to animals receiving more or less (even none) of the intended dose. In some countries therefore such syringes are not permitted in vaccination campaigns against FMD.

Post-vaccination monitoring

Because many factors may influence the efficacy of routine prophylactic vaccination against FMD, it is widely appreciated that post-vaccination monitoring (PVM) based on serology is

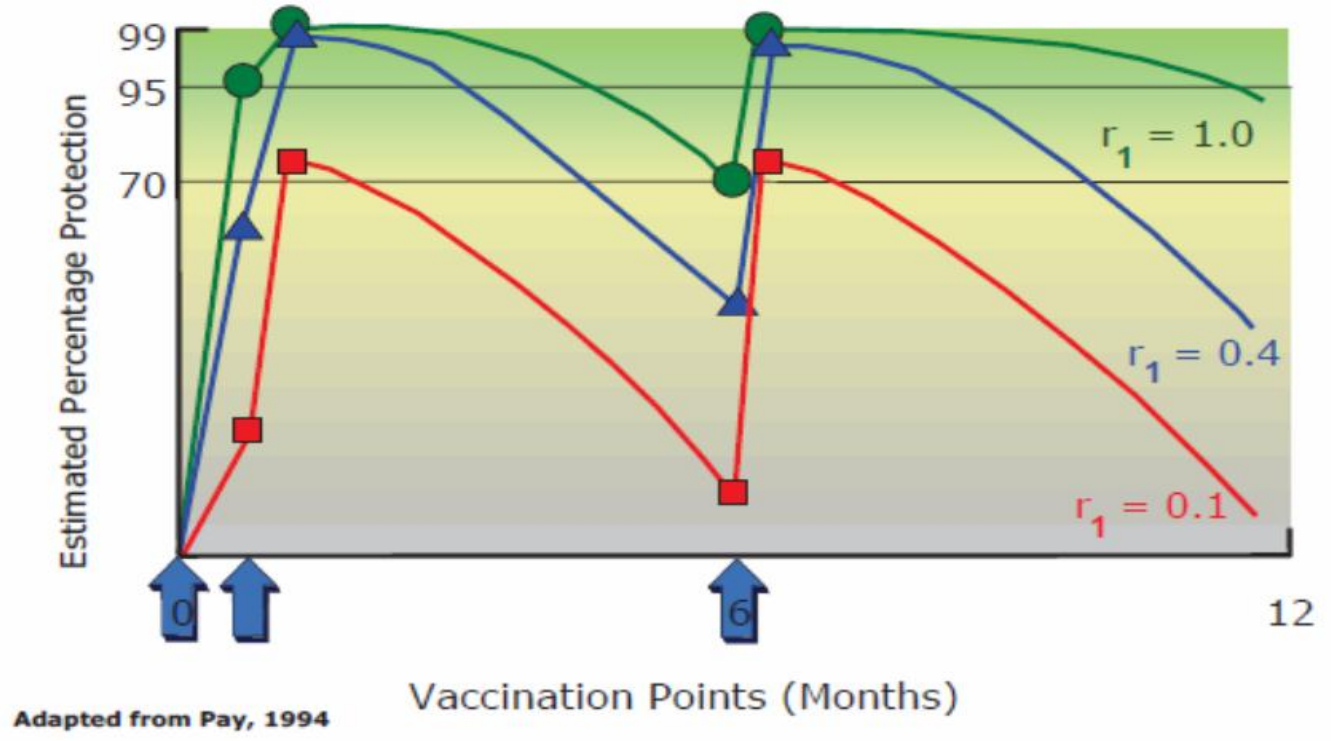

Figure 2b: Approximate graphic representation of percentage protection achievable by a SAT vaccine administered to cattle if challenged by a heterologous (r = 0.1) field virus of the same serotype **After: Pay, 1984**

vital for ensuring that vaccination campaigns are conducted efficiently and effectively. However, the conventional PVM process is unsuitable for determining the 'match' between field viruses and vaccine strains incorporated into commercially available vaccines. Measuring the 'match' thus requires a separate exercise based on determination of 'r-value' that can only be conducted in biologically secure, specialist laboratories.

In Zimbabwe very little PVM has been conducted in recent years (some results are available for 2003, 2010 & 2011), the paucity of data apparently being mainly due to a shortage of serological reagents. The available results also indicate unsatisfactory herd immunity levels (i.e. far below the norm of 70%) and limited information the follow up actions taken to investigate and rectify the reasons for the poor performance of the vaccine.

A possible complication

It has been pointed out in at least two publications that genomic diversity within SAT 2 viruses appears to have declined in recent years, although the reason for that has not been explained (Hall et al., 2014; Brito et al., 2016). An obvious possibility (but by no means proven) is that vaccines containing the same vaccine strains have been used widely in southern Africa for several decades now and it could be that this has resulted in selection pressure against field viruses that are antigenically similar to the vaccine strains, thereby favouring viruses that differ antigenically from the vaccine strains. It should be remembered that FMD in cattle with SAT 2 viruses has historically occurred more frequently in southern Africa than is the case for the other two SAT serotypes (Thomson & Bastos, 2004). This issue requires further investigation.

Conclusion

The use of vaccine against FMD can be effective but for that to be so requires that basic technical, logistical and financial factors need to be complied with in order for vaccination to be successful. This is especially important for the SAT serotypes because the available vaccines do not fulfil a number of criteria for effective vaccines and therefore can seldom, if ever, be relied upon as the sole control measure in FMD prevention. It is probable that these considerations are all too frequently overlooked in southern Africa with the result that very expensive and demanding control operations can prove to be the least efficient use of valuable resources.

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COMMENT/DISCUSSION

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